Aaron van Dorn (00:07):

Welcome to AJP Audio for April, 2024. I'm Aaron van Dorn. Today on the podcast, I spoke with Dr. Soonjo Hwang, a psychiatrist at the University of Nebraska Medical Center. Dr. Hwang and colleagues have a study in the April issue of the American Journal of Psychiatry, looking at the response to intranasally administered oxytocin in youths with severe irritability, one of the major reasons children are referred to psychiatric treatment, and a risk factor for disruptive behavior disorders. Afterwards, we'll hear from AJP editor-in-chief, Dr. Ned Kalin, about the rest of the April issue, which takes a close look at many other aspects of psychopathology in children and youths.

(00:37):

Dr. Hwang, your study investigated a potential treatment for irritability in children and adolescents, a major reason why children end up in psychiatric treatment. It's also been shown that children with chronic irritability are at risk for other long-term mental health problems, including anxiety, depression, and even suicide. What can you tell us about the relation to childhood irritability and the risk for other psychiatric disorders?

Dr. Soonjo Hwang (00:56):

So, irritability is a very common psychiatric symptoms in many diagnosis of children and adolescents, including attention deficit hyperactivity disorder, oppositional defiant disorder, conduct disorder, and disruptive mood dysregulation disorder. But also, it can present in many other psychiatric diagnosis of youth, such as major depressive disorder and anxiety disorders. And often it leads to the negative behavior outcome such as the anger outbursts and the aggressive behavior, which usually catch the attention from the teachers and their parents. So that's one of the reasons why they come to the psychiatric evaluation and treatment, and it's pretty well known, that leads to a negative outcome in their adulthood, such as substance use or other adulthood psychiatric disorders. So it's really important to recognize and address them promptly.

Aaron van Dorn (01:53):

Oxytocin is a neuropeptide hormone and lower levels of it have been reported in children with conduct disorders. Oxytocin has also been suggested as effective in inducing neural changes in children with irritability. As such, your group chose to look at the effects of intranasal oxytocin in children with irritability. What did you find?

Dr. Soonjo Hwang (02:09):

Really, interesting finding with what we did was that to some extent, it can induce clinical level changes of their symptoms, especially when we looked at the clinical global impression, means the measurement of overall severity of their symptoms related to irritability, such as a disruptive behavior and mood. It significantly improved by three weeks use of oxytocin, compared to placebo. Now, the irritability itself didn't reach the statistical significance to improve, but I think that's probably due to the fact that it was a short period of a clinical trial with a small number of participants. I'll say that this is a bit of a preliminary finding, that there's a promising future to study this more in the kids with irritability. So oxytocin is a very interesting hormone and it has been studied quite indeed significantly in the field of the psychiatry. Physiologically, as you may know, it is well known to induce the labor if you're pregnant. So for the pregnant women, that's one way to use, mainly by intravenous, to induce the labor.

(03:19):

But in our study, in terms of brain activation and brain function, it's a hormone known to develop the attachment and bonding. For example, again, if a woman delivers a baby, the woman's brain will produce a lot of oxytocin so she can develop the bonding attachment with the baby. Another very cool example is that if you get a dog, dog's brain as well as your brain will produce oxytocin so you can have a bonding behavior with each other. So it has been significantly used for that, in many psychiatric diagnosis such as schizophrenia, autism spectrum disorder, but then also a major depressive disorder, many anxiety disorders as well. At this point, I think the findings are, to put in the best way, inconclusive. So there's no major indication of oxytocin use for any specific clinical diagnosis.

(04:12):

I think, again, there are two limits that we're having, and again, I'm working on overcoming both of them. First is that the target engagement, meaning, what's the actual brain areas, can be significantly and meaningfully changed by the oxytocin, and what are the functions of those brain areas? So that's why we pick up the irritability, because indeed the irritability has some brain-level mechanisms that can be potentially targeted by oxytocin. And then as I said, our study verified that as a first step. For many other psychiatric diagnosis, maybe that should be the way to go for. Not target the categorical diagnosis as a whole, meaning let's treat the schizophrenia by oxytocin, let's kind of narrow down, say, Hey, there's irritability in those diagnosis, and they may share same mechanism that can be targeted by oxytocin in this case. I think that should be the future direction of clinical trial in psychiatry, not just for the oxytocin, for other interventions as well.

(05:19):

And then as I said, the second one is that many studies have used the 24 or 48 IU for certain period of time. Interestingly enough, again, they just follow one after another. But again, there's no really well established model for that, meaning what's the best dose to use for how long. So hopefully we'll get a more understanding of them so we can build a better design of a clinical trial in the future.

Aaron van Dorn (05:45):

Your group chose to look at oxytocin administered intranasally, and why did you choose that method as opposed to other? You mentioned previously that for inducing labor, it's often administered intravenously.

Dr. Soonjo Hwang (05:55):

Yeah, that's a great question. So the delivery of the oxytocin is also a really big question, because in case of a delivery, it has to go to the uterus. So the blood vessel is the best way to carry forward. Now, there's something, what we call the blood-brain barrier. So there's a barrier between outside of the body and the inside of the brain to protect it from outside [inaudible 00:06:20] because it's an important organ. And oxytocin is a peptide, meaning it's not small in terms of its size of molecule. So if you take it by mouth, it's going to be mostly breakdown in your digestive system. So there is what we call the olfactory bulb, inside of the nose, that's directly connected to the base of the brain. Because of the size of it, most of the clinical studies of oxytocin indeed are used via intranasal method for that reason. I think another pretty good example of the intranasal use for the same reason nowadays using widely, is ketamine for the depression.

Aaron van Dorn (06:58):

Are there known adverse effects to administering oxytocin, and in this case, extragenous oxytocin, especially intranasally?

Dr. Soonjo Hwang (07:04):

Yes. So it has been studied in various groups of people with psychiatric diagnosis. So we do have a fair amount of data on the common side effects of oxytocin. It seems like the most common side effect reported multiple times is the drowsiness. So kids become kind of sleepy by using it, and usually we were able to address that by moving the administration time to the night. So they take it before they go to bed. But also other side effects can occur, such as a headache, feeling dizzy or lightheaded. Sometimes their mood can be worse after using it, than better, but those are probably the most common side effects, but usually happens pretty rare. I would say most of them, less than 10 or 5%, and most of the time, they're self-limiting and mild. We believe that that's probably because it's not synthesized medicine, but it's a natural hormone.

Aaron van Dorn (08:00):

Your study used functional MRI scans prior to and after the administration of oxytocin. Was imaging useful in predicting an individual's response to it?

Dr. Soonjo Hwang (08:08):

So in this study, the importance of using the neuro imaging is what we call the target engagement, meaning it's also, of course, important to measure the reports of the symptoms and their changes from children and their parents. But at the same time, in our world of clinical studies and psychiatry, is really important to implement a methodology that actually capture the brain-level changes by an intervention, because it's really hard to do that just by asking questions. In this case, we were able to really capture some meaningful changes of the areas of the brain implicated in emotional control, emotion regulation, or emotional responding, by oxytocin. So indeed, kind of verify the target engagement.

Aaron van Dorn (08:53):

You mentioned this is a preliminary finding and a preliminary study, but are there any immediate clinical implications for your findings?

Dr. Soonjo Hwang (08:58):

Yeah, so we're kind of far away from that. It's not indicated to use it for irritability at this point, and it's not FDA approved for that indication, and I think it's a kind of first step to move towards that. So if we can study more the safety and efficacy of this, then it could be potentially another good modality to treat the irritability in children and adolescents. As you may know, there are options of treatment, such as medication or therapy or behavior intervention. All of them have limitations. Medications can come up with a side effect, the behavioral intervention or counseling takes time and effort. So we really need some new tools that can address this significant issue in children and adolescents. So, hopefully this will be the first step towards that.

Aaron van Dorn (09:49):

What were the limitations of your study?

Dr. Soonjo Hwang (09:51):

So as I said, the major limitation was probably the small number of adolescents and kids that participated, and also the relatively shorter duration of the intervention. That's most of the time, the

limits of many clinical trials. So we really need further study to expand from there with a larger sample and also longer duration of study.

Aaron van Dorn (10:13):

What's next for your research?

Dr. Soonjo Hwang (10:14):

Yeah, so what I'm doing actually, based on from this data, is to establish what we call dose response relationship and pharmacokinetics of oxytocin for this population. Interestingly enough, we decided to use a dose of 24 international IU. So that's how you measure the amount of oxytocin IU. 24 is pretty commonly used in many other clinical trials, but interestingly enough, there's no solID data on how much that can be actually delivered to the body and then how that's also delivered to the brain. So that's what we call the pharmacodynamics and pharmacokinetics of oxytocin. So in our current study, by using different doses including 24 but lower and higher dose as well, to see how we can establish those model to move forward the more meaningful and effective clinical trial.

Aaron van Dorn (11:10):

Well, Dr. Hwang, thank you for taking the time to speak with us, today.

Dr. Soonjo Hwang (11:12):

Thanks.

Aaron van Dorn (11:13):

Up next, Dr. Ned Kalin.

(11:15):

Dr. Kalin, welcome back to AJP Audio for April, 2024.

Dr. Ned Kalin (11:18):

I'm happy to be here with you, Aaron.

Aaron van Dorn (11:19):

The April issue of AJP takes a close look at the psychopathology of children and youth. Earlier in the podcast, I spoke with Dr. Soonjo Hwang. Dr. Hwang and colleagues investigated the response to intranasally administered oxytocin in youth with severe irritability. How does that fit in with its theme?

Dr. Ned Kalin (11:33):

First, let me say I'm particularly excited about this issue, because of its focus on youth psychopathology, treatment, parenting, and intergenerational transmission of psychopathology. This is really important because as we continue to understand more about psychiatric illnesses, we're really developing a neurodevelopmental perspective with an understanding that most illnesses begin early in life, with the risk to develop more severe symptoms later in life. And this issue is really focused on and dedicated to those types of themes. The paper that is focused on intranasal oxytocin you just referred to, is a really interesting paper that attempts to see if the administration of oxytocin intranasally has a positive impact on reducing irritability and also affecting brain function in youth that have externalizing and disruptive

mood types of disorders. So this is a study, a clinical trial, and it was a relatively small trial in youth that had either ADHD, oppositional defiant disorder, conduct disorder, or disruptive mood dysregulation disorder, and had significant irritability associated with all of that.

(12:48):

And basically 25 youth received intranasal oxytocin over a three week period, daily, and another 25 received placebo intranasally, daily. Primary outcome measures were an irritability scale and also scale of global functioning. What's important to note is that when you give oxytocin intranasally, it can directly get into the brain, and we know that in the brain there are receptors for oxytocin that actually mediate its effects. Oxytocin is well known in blood and in the periphery, to affect various physiological functions including lactation, childbirth as far as the uterus goes, [inaudible 00:13:30] contractions and clamping down and a whole bunch of other things. But in the brain, we now know that it has a lot to do with social attachment, bonding, things like that. So in this particular trial, the idea here was to see whether or not oxytocin administered intranasally would be therapeutic for these individuals. And the general outcome was that it did not show a significant effect on the irritability measure for which it was initially thought to impact or was hypothesized to impact, but did show a positive effect on the clinical global impression scale, which is this broader scale of function and symptoms.

(14:07):

So some hope here for it being effective in these individuals, but apparently not reducing irritability, at least as measured by the scale. But also, and importantly, in a subset of these participants, brain function was measured and there were significant changes in a variety of cortical areas, including regions in the prefrontal cortex and the cingulate cortex, all of which frequently have to do with emotion regulation. So this is a very early study. It's preliminary in nature, but it holds promise for the use of oxytocin administered intranasally. And I think we'll see more studies coming out to look at this.

Aaron van Dorn (14:43):

Keeping on the theme of irritability in youth, we have a review from Leibenluft and colleagues, also looking at the subject.

Dr. Ned Kalin (14:48):

Yeah, so this, we started off the issue with this review because it really sets the stage for psychopathology in youth, and also very much is aligned with this paper that I just discussed about trying to treat irritability. This is a really, really nice review that I encourage our readers to take a look at. It lays out the issues related to irritability, thinking about what is pathological irritability and what is not, what is age appropriate, things like that, but it also gives a sense of how to measure irritability, the importance of measuring it in clinical practice, the trans-diagnostic nature of it across various childhood disorders, and also gets into its genetics and its treatment. So a really useful up-to-date review on a symptom that frequently is overlooked but is very important from the standpoint of the experience of youth, as well as impacting their function.

Aaron van Dorn (15:39):

Next, we have an article from Aggarwal and colleagues, looking at the sex-specific micro architectural alterations in pre-adolescent children with anxiety disorders.

Dr. Ned Kalin (15:47):

So, white matter is that part of the brain that is related to the wiring and the connectivity of the wiring. White matter or the myelin sheath that covers neurons, is critical from the standpoint of the effective neuronal signaling between brain regions and the alignment of brain regions in relation to their function with each other. Now, for full disclosure, I'm a coauthor on this paper, so I have a bit of a bias about the relevance of this paper. But that aside, what we did in this study that was first authored by a former student of mine, the Nicole Agarwal, was to do a mega analysis so that we looked at all of the patients that we've studied over the years, that have anxiety disorders. These are eight to 12-year-old pre adolescents that are unmedicated, and compared parameters of white matter, using imaging to 132 age sex match controls that didn't have psychiatric illnesses.

(16:44):

And what we found was consistent with earlier work, where we found reductions in white matter, the integrity of white matter, as using a measure called fractional anisotropy. But what was really interesting about this is that we found this to occur in boys and not in girls, in this study. And so this suggests that boys may have more alterations in white matter, these are boys with anxiety disorders, than girls. This could be important in the pathophysiology of the illness. I should point out that one of the areas that was affected is the uncinate fasciculus, which is a white matter tract that connects critical regions of the brain that have to do with emotional experience, expression, and regulation, the prefrontal cortex with such structures as the amygdala and the medial temporal lobe.

(17:31):

We also know from earlier work that there are some more subtle effects in girls. So it's not like girls are completely unaffected, but in this large sample, we did not find any effects in girls, but we did in boys. This is important too because the sample was in pre-adolescent children before they were sexually mature, suggests that there are sexually dimorphic differences in some of the alterations in the brain that are associated with anxiety disorders. And interestingly enough, and importantly, white matter is actually plastic, so that it changes with experience, it changes in response to some medications. And if white matter and its integrity is important in the pathophysiology of anxiety disorders, it's interesting that it is plastic, because that suggests that it could be modified either by experience or with drugs, and actually might be a potential treatment target at some point.

Aaron van Dorn (18:22):

Pezzoli and colleagues took a look at negative parenting in its potential impact on callous and unemotional traits in children in mid to late childhood.

Dr. Ned Kalin (18:28):

This is an interesting study in a unique sample of over 9,000 twin pairs, half of which were monozygotic. By using twin pairs, one can analyze heritable or genetic influences because of the differences in the relatedness between monozygotic twins, which were roughly 100% similar in genetics, as to dizygotic twins, which only share half the genes. And what these investigators were interested in looking at, was the genetics of callous, unemotional traits as they relate to parental genetics and relate to parental styles of parenting. Now, why are callous, unemotional traits important? They're important because these traits which have to do with a lack of social awareness, a lack of interest in social interactions, some callousness in relation to things that happen socially, lack of concern perhaps, and so on. These are all markers, when extreme, of the risk to develop conduct disorder and antisocial personality disorders.

(19:37):

So by better understanding the development of callous, unemotional traits, we can get a better understanding, hopefully, of some of the factors that involve a greater risk to develop conduct disorder and antisocial personality disorders. So in this well-characterized sample of twins that were longitudinally studied, the bottom line was the genetics seemed to account for most of the variants in individual's development of callous, unemotional traits when they were assessed on average or they were assessed at seven, nine, and 12 years of age. Also, genetics seem to be involved in parenting styles from a standpoint of parents' negative feelings and discipline towards children. So it's really interesting that genetics also be involved with that. But importantly, these two did not seem to be related, so that there was not much of an impact when the authors did the analysis of parental discipline and negative feelings on the development of the child's callous, unemotional traits. And that was the hypothesis, that they would find that there was an impact.

(20:42):

Now, this has to be taken with a grain of salt, and we have a really nice editorial by Dr. Paul Frick, from Louisiana State University, where he has a pretty nuanced discussion of the relations between parenting styles and development of these types of traits. He points out that there are many other parental issues that could be important and other studies been shown to be important, including looking at the amount of warmth that parents have, and also other interactions between parents and children. So it's not like all parenting isn't important in the development of traits, but more specifically in this study, negative feelings that the parent had, and their discipline, did not appear to have a significant impact on the children's [inaudible 00:21:26] traits.

Aaron van Dorn (21:27):

Kendler and colleagues looked at the risk pattern for psychiatric and substance use disorder in the children of parents with alcohol use disorder. What can you tell us about that?

Dr. Ned Kalin (21:34):

Now, we already know that alcohol use disorder, in a significant way, is heritable and genetic, but this is a study that looked into not only the heritability, but also questions related to whether or not the mom or the dad that was affected, had more of an influence in the children's development of alcohol use disorder, and whether or not there were differences in the heritability of the child from the standpoint of the child's sex. So, would females or males be more likely to inherit this from their parents. Now, the reason they even got into this issue is because it's known that there's a higher incidence of alcohol use disorder in males, compared to females. And so they wanted to begin to try to ask whether or not there were sex-related differences in the genetic transmission of alcohol use disorder. And actually in this extremely large sample that involved over 1.2 million offspring from a Swedish registry sample, they did not find that.

(22:32):

They certainly did find that alcohol use disorder was heritable, that if parents had alcohol use disorder, the risk in children to develop it was increased about 2.3 fold. If both parents had it, it was increased about 4.6 fold. So dramatic increase in risk to develop alcohol use disorder if your parents have it. And also there was an increased risk for developing other illnesses that they looked at like ADHD and major depression, although the risk was much less. They did not find evidence, however, for sex-related differential transmission of alcohol use disorder to offspring. And while they did find increased risk to develop alcohol use disorder, externalizing disorders, and internalizing disorders, in offspring, they did not find evidence for sex-specific familial transmission of alcohol use disorder.

Aaron van Dorn (23:23):

Finally, we have a paper from Hou and colleagues, who investigated N2 response in youth with psychosis risk syndrome and its association with clinical outcomes.

Dr. Ned Kalin (23:30):

A major theme in psychiatry has been and continues to be trying to find biomarkers that predict the risk to develop disorders, or predict which medications to use, or predict treatment response. And this is a study that looks a neurophysiological measure, as has been done frequently in the past, to understand whether or not it can predict youth at risk to develop psychotic disorders. This is a study done with youth from Chinese universities, and 122 college-aged students, freshmen were identified that were thought to have the psychotic risk syndrome. I won't go into detail how about they define that. They compared those responses to 50 individuals that had major depression and some anxiety and 51 control individuals that apparently did not have any psychiatric illnesses. And what they used was what was called an oddball paradigm. This is a paradigm where you present a stimulus on a regular basis, in this case, a visual stimulus, and then once in a while, in an unexpected way, present a visual stimulus that the individual is not expecting, maybe one of these or two of these, and this uncertain presentation of the unexpected stimulus, elicits a specific electrophysiological response in certain brain regions related to attention.

(24:51):

And one of the responses that they looked at, what's termed the N2 response, and this is a response that occurs approximately 200 milliseconds after the stimulus is presented. And typically there's a reduction in amplitude in this response that occurs. So it's a negative wave. And what they found was that in individuals that were at risk to develop psychotic disorders, or the psychosis risk group, that the N2 amplitude, or the height of the wave, was significantly less negative in the psychosis risk group than it was in the control group. So they found this alteration. They then followed these individuals for one year, and they looked to see how many of these individuals that were at risk, actually converted to psychosis, and what happened to this biomarker.

(25:39):

And what they found was is that in these individuals that were at risk, roughly 20% of them went on to develop psychoses, and they actually found that in those individuals, that this biomarker, this N2 negative wave, the amplitude of that was even more abnormal than it was in the risk group. They also found that in those individuals that actually got better, that moved from the risk group to sort of a more normal group, that this altered finding in this N2 amplitude actually seemed to get somewhat better. So this shows some promise for this as a biomarker for root marking risk of those that may develop psychotic disorders. But again, it's not a particularly strong finding. It's in a relatively small sample. And in the editorial provided by Drs. Gregory Light and Neil Swerdlow from the University of California, they talk about this finding in the context of other work, and they also really provide a very thoughtful discussion that addresses the challenges about finding reliable biomarkers and also the challenges that are associated with developing new treatments for schizophrenia.

Aaron van Dorn (26:47):

Well, Dr. Kalin, thank you once again for joining us.

Dr. Ned Kalin (26:49):

Thank you very much. It's a pleasure to be with you, Aaron.

Aaron van Dorn (26:52):

That's all for this month's AJP audio. But be sure to check out the other podcasts from the APA. The Medical Mind Podcast recently featured a limited series from the APA's Women's Psychiatrists Caucus, in which women's psychiatric leaders from across the country were interviewed about their experiences. One of the interviews featured Dr. Lisa Dixon, editor of Psychiatric Services and co-host of Psychiatric Services: From Pages to Practice, another APA Publishing podcast, all of which you can find at psychiatryonline.org/podcasts or wherever you get podcasts.

Speaker 5 (27:20):

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